

A41
cont (2) injecting said implant into the animal body.

Please cancel claim 16 without prejudice or disclaimer.

AS
19. (Amended) The method of Claim 18 wherein said biologically active composition comprises [MGA] melengestrol acetate, a combination of [MGA] melengestrol acetate and [TBA] trenbolone acetate or a combination of [MGA, TBA] melengestrol acetate, trenbolone acetate and estradiol.

20. (Amended) The method of Claim 19, wherein the [MGA] melengestrol acetate is contained in each delivery vehicle in an amount of from about 5 to about 200 mg per delivery vehicle.

Remarks

Claims 1, 4-15 and 17-25 are pending in the present application with claims 1, 8, 9, 11, 13, 19 and 20 having been amended by this amendment and claims 2,3 and 16 having been cancelled by this amendment. Applicants respectfully request reconsideration of the matter.

Applicants have amended claims 8, 9, 11, 19 and 20 order to overcome the indefiniteness rejection under 35 U.S.C. §112, second paragraph and have inserted the limitations of claim 2 into claim 1 except for the embodiment which defines the first vehicle as having "very thin" walls. It is respectfully submitted that no new matter has been inserted by the amendments. The amendments to these claims were not made in furtherance of patentability as defined by the United States Supreme Court in the Hilton Davis Chemical Co. v. Warner Jenkinson Co. case. In light of the amendments to the claims, Applicants respectfully request that the rejection to claims 2, 8, 9, 11, 19 and 20 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claims 1-25 have been rejected as being unpatentable under 35 U.S.C. §103 over US 5,288,496 and US 5,654,496 and further in view of US 4,652,411. This rejection is respectfully traversed.

In order for the Examiner to sustain the burden of a *prima facie* rejection it must be demonstrated that: (1) the prior art relied upon, coupled with the knowledge generally available in the art at the time of invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify or combine references; (2) the proposed modification must have had a reasonable expectation of success at the time the invention was made; and (3) the prior art combination of references must teach or suggest all the limitations of the claims. All of the teachings, suggestions and expectation of success must come from the prior art, and not Applicants' disclosure.

With respect to independent claims 1 and 13, and those dependent therefrom, Applicants have limited their claims to embodiments where the first delivery vehicle is selected from the group consisting of encapsulants where the coating wall material is highly soluble in body fluids, porous or freeze-dried solid compositions, solid tablets or pellets containing a disintegrating agent which causes the solid tablet or pellet to rapidly break down when in body fluids, solid tablets or pellets containing said biologically active material in fine or micronized particle sizes, an osmotic delivery system where the osmotic system is such that a substantial amount of the active is released upon implantation and mixtures thereof; and wherein the second delivery vehicle is selected from the group consisting of encapsulated solutions or suspensions, biodegradable solid substances, conventional tablet/pellet ingredients, conventional tablet/pellet ingredients coated with a polymeric membrane to control release, conventional tablets or pellets containing said biologically active material having large particle sizes, matrix-tablets based on gel-forming excipients, matrix-type systems based on non-biodegradable polymers, membrane-type systems based on non-biodegradable polymers, matrix-type systems based on biodegradable polymers, matrix-type systems implant based on lipidic excipients, mass transfer systems based on osmotic pressure pumping through a hole in an impermeable coating and mixtures thereof. As these delivery vehicles are nowhere suggested nor disclosed in the prior art references, the references cannot be properly applied as against the instant claims.

More specifically, both of the primary references disclose the use of specially designed microparticles to obtain the delivery vehicles of their invention. The microparticles have to be made from known biodegradable synthetic polymers, casein, albumin, and waxes. The process involves solubilization of polymer and active in an organic solvent system, emulsification of the solution, removal of solvent by

evaporation, and collection of the microparticles. Various release rates are obtained by altering the size or size distribution of the microparticles used. The dosage is injected by first suspending the particles in water or saline and then injecting at site.

By direct comparison, the use of microparticles as delivery vehicles do not comprise any aspect of the claimed invention.

Moreover, referring to Lewis at Col. 3, lines 12-15, the concept of multiphasic release is explained as describing a product having a faster release of active to an animal based upon the growth of the animal. Accordingly, what is desired is that a predetermined amount of active be administered based upon the size of the animal (i.e., more drug is delivered as the animal gets larger). By comparison, in the instant invention, the differential release is directed to both immediate release of active (to provide an instantaneously pharmacological effect) and sustained release of active (to provide a sustained pharmacological effect).

The secondary reference (Okada et al.) only discloses the desirability of developing a sustained release pharmaceutical composition. However, the Okada et al. reference nowhere discloses nor contemplates differential release of the same pharmaceutically active agent via the use of discrete delivery vehicles. In direct comparison, applicants' claimed invention is specifically directed to differential release of the same pharmaceutically active agent via the use of discrete delivery vehicles. As such, Okada et al. cannot be used to negative patentability of the claimed invention.

In addition to the arguments as presented above, applicants respectfully submit that independent claim 11, and dependent claim 12 are additionally patentable as none of the cited references disclose or suggest the use of one or more pellets or tablets containing a disintegrating agent with one or more pellets or tablets not containing a disintegrating tablet to administer melengestrol acetate to a host.

Accordingly, it is respectfully submitted that the rejection of claims 1-25 as being unpatentable under 35 U.S.C. §103 over US 5,288,496 and US 5,654,496 and further in view of US 4,652,411 must be withdrawn as a matter of law.

If there are any questions regarding this Amendment, the Examiner is cordially invited to contact the undersigned attorney at (616) 833-1861. A Notice of Allowance is respectfully solicited.

Respectfully submitted,



Andrew M. Solomon, Attorney
Registration No. 32,175

Date: 23 Apr 00

Pharmacia & Upjohn Company
Global Intellectual Property
301 Henrietta Street
Kalamazoo, Michigan 49001

Telephone No. (616) 833-1861 or (616) 833-9500
Telefax No. (616) 833-8897 or (616) 833-2316

W:\AMS\6231amdt.doc